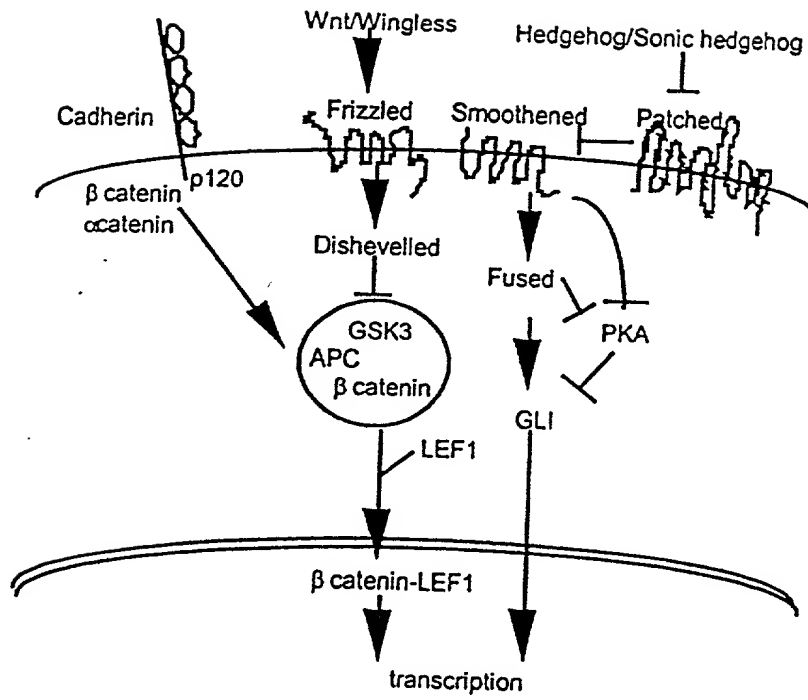


Figure 1



09847402-050104

Figure 2a

# Alignment of several frizzled family members

	→	amino terminal domain
fz3/mouse	-----	MAVSWIVFDLWLLTVFLG---QIGGHS-----LFSCE
fz4/mouse	-----	MAWPGTGPS---SRGAPGGVGLRLGLLLQFLLLLRPTLGFGD-----EEERRCD
fz8/mouse	-----	MEWGYL-----LEVTSLLAALAVLQRSSG-AAAASAK-----ELACQ
fz5/human	-----	MARPDP-----SAPPSLL--LLLLLAQLVG-RAAAASK-----APVCQ
fzd9/human	-----	MAVAPLRGALLLWQLLAAGGALEIGRFD-----PERGRG-----AAPCQ
fz1/rat		LEAPLLLGVRAQPAG---QVSG-PGQQRPPPPQPQGG--QQYNGERG--ISIPDHGYCQ
fz2/rat	-----	MRARSAL---PRSALPRLLLPLLLLPAAGP--AQFHGEKG--ISIPDHGFCQ
fz/Dros		ILPTLIQGVQRYDQS---PLDASPYRSGGGLMASSG--TELDG-----LPHHNRCE
fz2/Dros/		GLVLLLTSCRADGPL-----HSADHGMGGMGMGGHGLD-ASPAPGYGVPAPKDPNLRCE
		*:
		CRD
fz3/mouse		PITLRMCQDLPYNTTFMPNLLNHYDQQTAALAMEPFHMPVNLDCSRDFRPFLCALYAPIC
fz4/mouse		PIRIAMCQNLGYNVTKMPNLVGHLELQTDALQLTTFTPLIQYGCSSQLQFFLCSVYVPMC
fz8/mouse		EITVPLCKGIGYNYTYMPNQFNHDTQDEAGLEVHQFWPLVEIQCSDDLKFFLCSMYTPIC
fz5/human		EITVPMCRGIGYNLTHMPNQFNHDTQDEAGLEVHQFWPLVEIQCSDDLKFFLCSMYTPIC
fzd9/human		AVEIPMCRGIGYNLTHMPNLLGHTSQGEAAAEAEFAPLVQYGCCHSLRFFLCSLYAPMC
fz1/rat		PISIPLCIDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVC
fz2/rat		PISIPLCIDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFLLCSMYAPVC
fz/Dros		PITISICKNIPYNMTIMPNNLIGHTKQEEAGLEVHQFAPLVKIGCSSDDLQFLCSLYVPVC
fz2/Dros/		EITIPMCRGIGYNMTSFPNEMNHETQDEAGLEVHQFWPLVEIKCSDDLKFFLCSMYTPIC
		: : * . : ** : ** . * * * : : * : : * : : ** : **
		CRD
fz3/mouse		M-EYGRVTLPCCRLCQRAYSECSKLMEMFG-VPWPEDMECSRFPDCE-EPYPRIVDLN--
fz4/mouse		TEKINIPIGPCGGMCLSVKRRCEPVLREFG-FAWPDTLNCSKFPPQN-DHNHMCMEGP--
fz8/mouse		LEDYKKPLPPCRSVCERAKAGCAPLMRQYG-FAWPDRMRCDLRLEQG-NPDTLCMDYN-R
fz5/human		LPDYHKPLPPCRSVCERAKAGCSPLMRQYG-FAWPERMSCDLRPLVGRDAEVLCMDYN-R
fzd9/human		TDQVSTPIPACRPMCEQARLRCAPIEQFN-FGWPDSLDCARLPTRN-DPHALCMEAPEN
fz1/rat		T-VLEQALPPCRSLCERA-QGCEALMNKFG-FQWPDTLKCEKFPVHG--AGELCVGQNTS
fz2/rat		T-VLEQAIPPCRSICERARQGCEALMNKFG-FQWPERLRCEHFPRHG--AEQICVGQNH
fz/Dros		T-ILERPIPPCRSLCESA-RVCEKLMKTYN-FNWPENLECSKFVHG--GEDLCVAENTT
fz2/Dros/		LEDYHKPLPVCRSVCERARSGCAPIMQYS-FEWPERMACEHLPLHG-DPDNLCMEQPSY
		* : * . * ** : * : *
		:
		:
fz3/mouse	-----	LVGDPTTE---
fz4/mouse	---GDEE-----	VPLPHKTP-
fz8/mouse		TDLTAAAPSPRRLLPPPPPPGEQPPSGSGHSRPPGARPPHGGSSRSGDAAAAPPSRGG
fz5/human		SEATTAPPRP---FPAKP---TLP--G-----PP-----G---APAS-GG
fzd9/human		ATAGPAEPHK---GLGM---LP-----VAPRPAPPPG
fz1/rat		DKGTPTPSL-----L-----PEFWTSNPQHG
fz2/rat		EDG--TPAL-----L-----TTAPPSGLQPG
fz/Dros		SSA-----STAATPTRSVA
fz2/Dros/		TEAGSGGSSG---GSGG---SGSGSGSGGKRKQGGSGSGSGAGGSSGSTSTKPCR-GR

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Figure 2b

amino terminal domain continued

		← TM1 →
fz3/mouse	YSFLHVRDCSPPCPN-----MYFRREELSFARYFIGLISIICLSATLFTFLTLIDVTR	
fz4/mouse	--LNCVLKCGYDAG-----LYSRSAKEFTDIWMAVWASLCFISTTFTVLTLIDSSR	
fz8/mouse	-KTGQIANCALPCHN-----PFFSQDERAFTVFWIGLWSVLCFVSTFATVSTFLIDMER	
fz5/human	-RTGQVPNCAVPCYQ-----PSFSADERTFATFWIGLWSVLCFISTSTTVATFLIDMDT	
fzd9/human	--RSCAPRCGPGVEV-----FWSRRDKDFALVWMAVWSALCFFSTFTVLTLFLEPHR	
fz1/rat	LGEK---DCGAPCEPTKVYGLMYFGPEELRFSRTWIGIWSVLCFASTLFTVLTYLVDMMR	
fz2/rat	LGER---DCAAPCEPARPDGSMFFSHHTRFARLWILTWSVLCFASTFTVTTLVAMQR	
fz/Dros	VGGKDLHDCGAPCH-----AMFFPERERTVLRVWGSWAACVASCFTVLTLFLIDSSR	
fz2/Dros/	QRIAGVPNCGIPCKG-----PFFSNDEKDFAGLWIALWSGLCFCSTLMTLTTFIIDTER	
	* : : *	

	← TM2 →	extracellular domain loop 1
fz3/mouse	FRYPERPIIFYAVCYMMVSLIFFIGFLE-DRVACNASSP-----	
fz4/mouse	FSYPERPIIFLSMCYNIYSIAXIVRLTVGRERISCDF-----	
fz8/mouse	FKYPERPIIFLSACYLFSVGYLVRVLVAGHEKVACSGGAPGAGGRGGAGGAAAAGAGAAG	
fz5/human	FRYPERPIIFLSACYLCVSLGFLVRLVVGHASVACS-----	
fzd9/human	FQYPERPIIFLSMCYNVYSIAFLIRAVAGAQSACD-----	
fz1/rat	FSYPERPIIFLSGCTAVAVAYIAGFLE-DRVVCNDKFAE-----	
fz2/rat	FRYPERPIIFLSGCTMVSVAIYAGFVLQ-ERVVCNERFSE-----	
fz/Dros	FRYPERAIVFLAVCYLVGCAYVAGLGAG-DSVSCREPFPPPVK---LG-----	
fz2/Dros/	FKYPERPIVFLSACYFMVAVGYLSRNLQNEEIIACDG-----	
	* **** : : * . ** . :	

	← TM3 →
fz3/mouse	-----AQYKASTVTQGSNKK-ACTMLFMVLYFFTMAGSVWVWVILTITWFLA
fz4/mouse	-----EEAAEPVLIQEGKNTGCAIIIFLLMYFFGMASSIWWVILTLTWFLA
fz8/mouse	RGASSPGARGEYEELGAVEQHVRVETGTPALCTVVFLLVYFFGMASSIWWVILSLTWFLA
fz5/human	R-----EHNHIHYETGTPALCTIVFLLVYFFGMASSIWWVILSLTWFLA
fzd9/human	-----QEAGALYVIQEGLENTGCTLVFLLLYFFGMASSLWVWVLTTLTWFLA
fz1/rat	-----DGARTVAQGTKE-GCTILFMMLYFFSMASSIWWVILSLTWFLA
fz2/rat	-----DGYRTVGQGTKE-GCTILFMMLYFFSMASSIWWVILSLTWFLA
fz/Dros	-----RLQMMSTITQHRQTTCTVLFMALYFCCMAAFWWSCLAFWFLA
fz2/Dros/	-----LLLRESSTGPHSCTLVFLLTYFFGMASSIWWVILTITWFLA
	: * : : : ** : : : *

	← TM4 →	extracellular domain loop 2
fz3/mouse	AVPKWGSEAIKALLHASAWGIPGTLTIILLAMNKIEGDNISGVCVGLYDVLDALRYF	
fz4/mouse	AGLKWGHEAIEMHSSYFHIAAWAIPAVKTIVILIMRLVDADELTLGLCYVGNQNLDAITGF	
fz8/mouse	AGMKWGNEAIIAGYSQYFHLAAWLPSVKSIAVLALSSVDGDPVAGICYVGNQSLDNLRGF	
fz5/human	AAMKWGNEAIIAGYQYFHLAAWLIPSVKSITALALSSVDGDPVAGICYVGNQNLNLSLRRF	
fzd9/human	AGKKWGHEAIEAHGSYFHMAAWGLPALKTIVILTILRKVAGDELTLGLCYVASTDAAALRGF	
fz1/rat	AGMKWGHEAIEANSQYFHLAAWVPAIKTITILALGQVDGDLVSGVCVGLNNDALRGF	
fz2/rat	AGMKWGHEAIEANSQYFHLAAWVPAVKTITILAMGQIDGDLVSGVCVGLNRLDPLRGF	
fz/Dros	AGLKWGHEAIEENKSHLFHLVAVVPAVQITISVLALAKVEGDILSGVCVGLDTHSLGAF	
fz2/Dros/	AGLKWGNEAIIKHSQYFHLAAWLIPVQSVAVLLLSAVDGDPIIGICYVGNLNPDLKTF	
	: ** . * : . ** ** * . : * : : : * : *	

09847102-050101



Figure 3

Sequence alignment of a portion of the aminoterminal extracellular region of human  
Frizzled receptors

HF21 VGQNTSDKGT---PSLLPEFWTSNPQHGGGGHGRG-----GFPGGAG----ASERGKFS CPR  
HF22 VGQNHSEDGA-----PALLTTAPPPGLQPGAGGTPG-----GPGGGGAPPRYATLEHPFHC  
HF23 LVDLNLAG-----EPTEGAPV-----AVQRDYG-----FWC  
HF24 CMEGPGD-----EE-----VPLPHKTPI-----QP  
HF25 CMDYNRSEATTAPPRPFPKPTLPG-----PPGA-----PASGG-----ECPAGGPFV-----CKC  
HF26 TFDPHTEF-----LGPQKKTE-----QVQRDIG-----FWC  
HF27 VGQNTSDGSGGPGGGPTAYPTAPYLPDLPFTALPPG-----ASDGRGRPAF-----PFSC  
HF28 CMDYNRTDLTTAAPSPPRRLPPPPP-GEQPPSGSGHGRPPGARPPHRGGGRGGGGDAAAPPARGGGGGKARPPGGGAAP---CEPGCQC  
HF29 CMEAPENA-TAGPAEPHKGLGMLPV-----APRPARPPG-----DLGP  
HF30 NYLCMEAPNN---GSDEPTRGSGLFPP-----LFRPQRPHSAQ---EHP

Figure 4

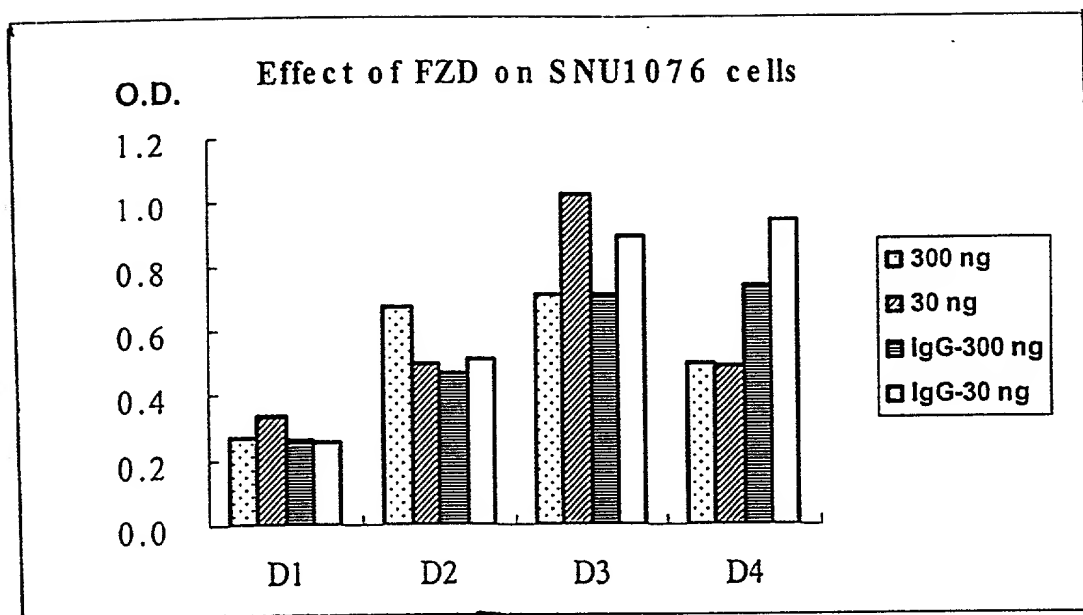


Figure 5

Effect of antibodies SNU 1076 Cells

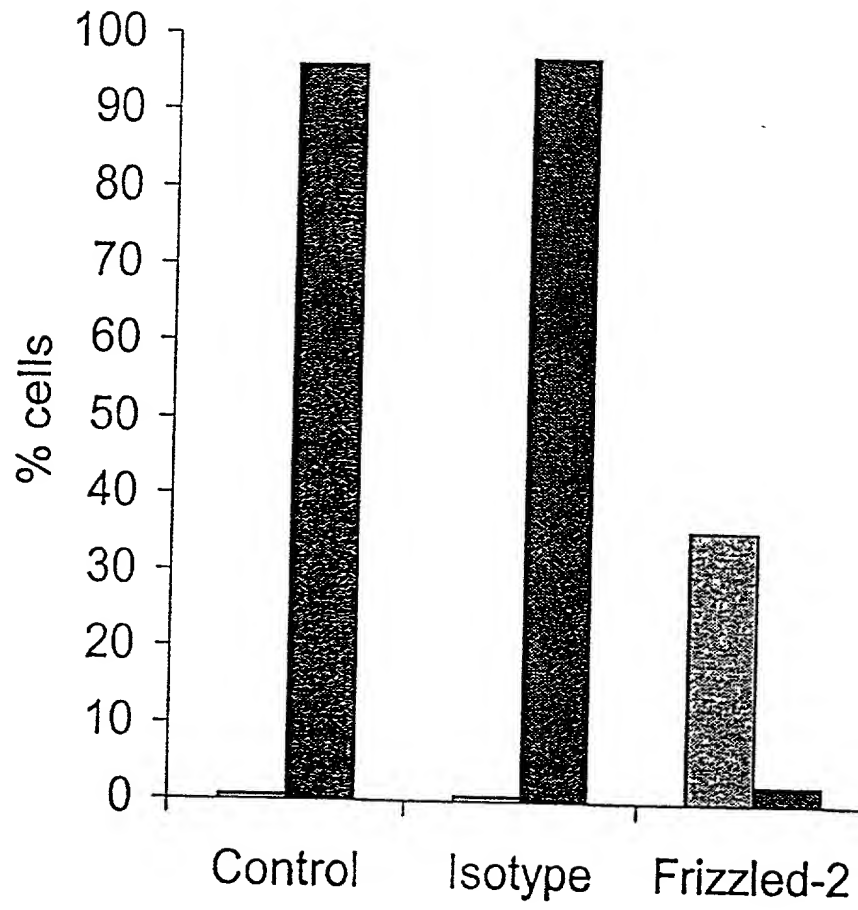


Figure 6

Effect of antibodies on SNU 1076 cells

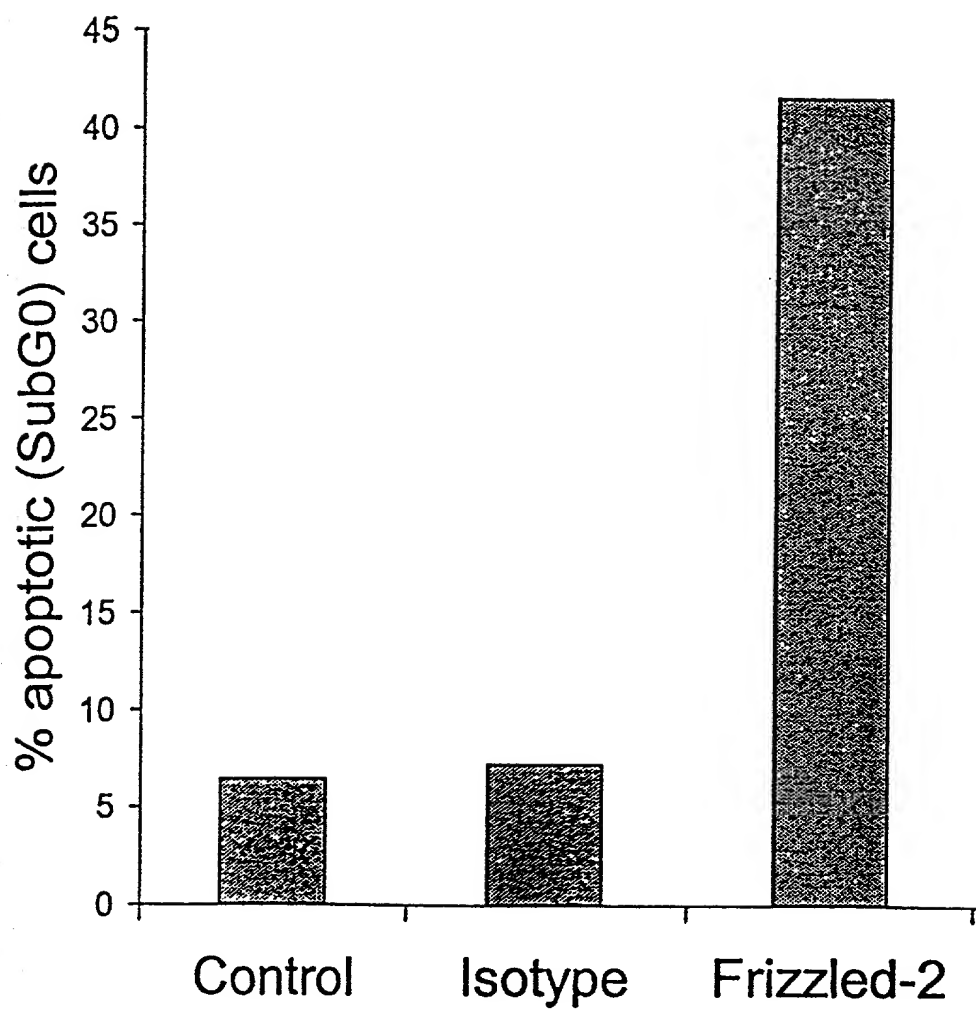






Figure 8a

→ amino terminal domain

HFZ1	MAEEEAPKKSRAAGGGASWELCAGALSARLAEEGSGDAGGRRRPPVDPRLRLARQLLLLLLW
MFZ1	MAEEAAPSESRAAGR-LSLELCALPGRREEVGHEDTASHRRPRADPRRWASGLLLLLLW
HFZ2	-----MRPRSALPRLLPLL
HFZ3	-----MAMTWIVFSLWPLTV
MFZ3	-----MAVSWIVFDLWLLTV
HFZ4	-----MAWRGAGPSVPGAPGGVGLSLGLLLQ
MFZ4	-----MAWPGTGPSSRGAPGGVGLRLGLLLQ
HFZ5	-----MARPDPSAPPSLL--LLL
HFZ6	-----MEMFTFLLTCI
MFZ6	-----MERSPFLLACI
HFZ7	-----MRDPGAAAPLSSLGLCALVLA
MFZ7	-----MRGPGTAASHSPGLCALVLA
HFZ8	-----MEWGYLLEVTSLLAALAL
MFZ8	-----MEWGYLLEVTSLLAALAV
HFZ9	-----MAVAPL-RGALLWQLLA
MFZ9	-----MAVPPLLRGALLWQLLA
HFZ10	-----MQRPGPRLWLVLQ

HFZ1	LLEAPLLLGVRAQAAGQGPGPGQPPPPPPQQQSGQQYNGERGISVPDHGYCQPIS
MFZ1	LLEAPLLLGVRAQAAGQVSG---PGQQAPPPPPQQQSGQQYNGERGISIPDHGYCQPIS
HFZ2	LLPA-----A-----GPAQFHGEKGISIPDHGFCQPIS
HFZ3	FMGHI-----GGHSLFS-----CEPIT
MFZ3	FLGQI-----GGHSLFS-----CEPIT
HFZ4	LLLLLG-----PARGFGDEEE-----RRCDPIR
MFZ4	FLLLLR-----PTLGFGDEEE-----RRCDPIR
HFZ5	LAQLVG-----RAAAASKAPV-----CQEIT
HFZ6	FLPLL-----RGHSLFT-----CEPIT
MFZ6	LLPLV-----RGHSLFT-----CEPIT
HFZ7	LLGAL-----SAGAGAQPYPHGEKGISVPDHGFCQPIS
MFZ7	LLGAL-----PTDTRAQPYPHGEKGISVPDHGFCQPIS
HFZ8	LQRSSG-----AAAASAKELA-----CQEIT
MFZ8	LQRSSG-----AAAASAKELA-----CQEIT
HFZ9	AGGAAL-----EIGRFDPERGR---GAAPCQAVE
MFZ9	TGGAAL-----EIGRFDPERGR---GPAPCQAME
HFZ10	VMGSCA-----AISSMDMERP---GDGKCQPIE

\* : :

HFZ1	IPLCTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVCT-V
MFZ1	IPLCTDMAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVCT-V
HFZ2	IPLCTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVCT-V
HFZ3	LRMCQDLPYNTTFMPNLLNHYDQQTAAALAMEPFHPMVNLDCSRDFRPFLCALYAPICM-E
MFZ3	LRMCQDLPYNTTFMPNLLNHYDQQTAAALAMEPFHPMVNLDCSRDFRPFLCALYAPICM-E
HFZ4	ISMCQNLGYNVTKMPNLVGHQLTDAELQLTTFTPLIQYGCSSQLQFFLCVYVPMCTEK
MFZ4	IAMCQNLGYNVTKMPNLVGHQLTDAELQLTTFTPLIQYGCSSQLQFFLCVYVPMCTEK
HFZ5	VPMCRGIGYNLTHMPNQFNHDTQDEAGLEVHQFWPLVEIQSPDLRFFLCTMYTPICLPD
HFZ6	VPRCMKMAYNMTFFPNLMGHYDQGIAAVEMGHFLHLANLECSNFIETFLCKAFVPTCI-E
MFZ6	VPRCMKMTYNMTFFPNLMGHYDQGIAAVEMGHFLHLANLECSNFIETFLCKAFIPTCT-E
HFZ7	IPLCTDIAYNQITILPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVCT-V
MFZ7	IPLCTDIAYNQITILPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVCT-V
HFZ8	VPLCKGIGYNYTYMPNQFNHDTQDEAGLEVHQFWPLVEIQSPDLKFFLCSMYTPICLED
MFZ8	VPLCKGIGYNYTYMPNQFNHDTQDEAGLEVHQFWPLVEIQSPDLKFFLCSMYTPICLED

HFZ9 IPMCRGIGYNLTRMPNLLGHTSQGEAAAEALAEFAPLVQYGCHSHLRFFLCSLYAPMCTDQ  
 MFZ9 IPMCRGIGYNLTRMPNLLGHTSQGEAAQLAEFSPLVQYGCHSHLRFFLCSLYAPMCTDQ  
 HFZ10 IPMCKDIGYNMTRMPNLMGHENQREAAIQLHEFAPLVEYGCHGLRFFLCSLYAPMCTEQ  
 : \* : \*\* \* : \*\* . \* \* \* : \* : : \* . . . \*\*\* : \* \*

HFZ1 LEQALPPCRSLCERARQGCEALMNKFGFQWPDTLKCEKFPVHG--AGELCVGQNTSDKGT  
 MFZ1 LEQALPPCRSLCERARQGCEALMNKFGFQWPDTLKCEKFPVHG--AGELCVGQNTSDKGT  
 HFZ2 LEQAIPPCRSICERARQGCEALMNKFGFQWPERLRCEHFPRHG--AEQICVGQNHSEDA  
 HFZ3 YGRVTLPCRRLCQRAYSECSKLMEMFGVPWPEDMECSRFPDCE--EPYPRLVDLNLG---  
 MFZ3 YGRVTLPCRRLCQRAYSECSKLMEMFGVPWPEDMECSRFPDCE--EPYPRLVDLNLVG---  
 HFZ4 INIPIGPCGGMCLSVKRRCEPVLKEFGFAWPESLNCSEKFPQON--DHNHMCMEGPGD----  
 MFZ4 INIPIGPCGGMCLSVKRRCEPVLREFGFAWPDTLNCSKFPQON--DHNHMCMEGPGD----  
 HFZ5 YHKPLPPCRSVCERAKAGCSPLMRQYGFAPWPERMSCDRLPVLGRDAEVL CMDYRSEATT  
 HFZ6 QIHVVPPCRKLCEKVYSDCKKLIDTFGIRWPEELECRLQYCD--ETVPVTFDPHTEF---  
 MFZ6 QIHVVLPCKRLCEKIVSDCKKMDTFGIRWPEELECRLPHCD--DTVPVTSHPHTEL---  
 HFZ7 LDQAIPPCRSICERARQGCEALMNKFGFQWPERLRCEHFPRHG--AGEICVGQNTSDGSG  
 MFZ7 LDQAIPPCRSICERARQGCEALMNKFGFQWPERLRCEHFPRHG--AGEICVGQNTSDGSG  
 HFZ8 YKKPLPPCRSVCERAKAGCAPLMRQYGFAPWDRMRCDRLPEQG--NPDTLCMDYNRTDLTT  
 MFZ8 YKKPLPPCRSVCERAKAGCAPLMRQYGFAPWDRMRCDRLPEQG--NPDTLCMDYNRTDLTT  
 HFZ9 VSTPIACRPMCEQARLRCAPIEQNFNGWPDSDLCARLPTRN--DPHALCMEAPENA--TA  
 MFZ9 VSTPIACRPMCEQARLRCAPIEQNFNGWPDSDLCARLPTRN--DPHALCMEAPENA--TA  
 HFZ10 VSTPIACRVMCEQARLKCSPIEQNFNKPWPDSDLCRKL PNKN--DPNYLCMEAPNN----  
 . \* : \* \* : : . . . \*\* : : \* . : .

HFZ1 PT---PSLLPEFWTSNPQHGGGGHGRG-----  
 MFZ1 PT---PSLLPEFWTSNGQHGGGGYRG-----  
 HFZ2 -----PALLTTAPPPGLQPGAGGTPG-----  
 HFZ3 ---EPTGAPV-----A  
 MFZ3 ---DPTGAPV-----A  
 HFZ4 -----EE-----V  
 MFZ4 -----EE-----V  
 HFZ5 APPRPFPAKPTLPG-----PPGA-----PASGG-----  
 HFZ6 ---LGPQKKTE-----Q  
 MFZ6 ---SGPQKKSD-----Q  
 HFZ7 GPGGGPTAYPTAPYLPDLPTALPPG-----  
 MFZ7 GAGGSPTAYPTAPYLPDPPFTAMSP-----  
 HFZ8 AAPSPRRRLPPPPP--GEQPPSGSGHGRPPGARPPHRRGGGGGGDAAAPPARGGGGGGK  
 MFZ8 AAPSPRRRLPPPPPPGEQPPSGSGHSRPPGARPPHRRGGSSRSGDAAAAPPSSRGG----K  
 HFZ9 GPAEPHKGLGMLPV-----A  
 MFZ9 GPTEPHKGLGMLPV-----A  
 HFZ10 GSDEPTRGSGLFPP-----L

HFZ1 GFPGGAG---ASERKGFSCPRALKVPSYLYNHYFLGEKDCGAPCEPTKVYGLMYFGPEEL  
 MFZ1 GYPGGAG---TVERGKFSCPRALRVPSYLYNHYFLGEKDCGAPCEPTKVYGLMYFGPEEL  
 HFZ2 GPGGGGAPPRYATLEHPFHCPRVLKVPSYLSYKFLGERDCAAPCEPARPDGSMFFSQEET  
 HFZ3 VQRDYG-----FWCPRELKIDPDLGYSFLHVRDCSPPCP---NMYFR--REEL  
 MFZ3 VQRDYG-----FWCPRELKIDPDLGYSFLHVRDCSPPCP---NMYFR--REEL  
 HFZ4 PLPHKTPI-----QPGECHSVGTNSDQYIWKRSNLNVLKCGYDAGLY--SRSAK  
 MFZ4 PLPHKTPI-----QPGECHSVGSNSDQYIWKRSNLNVLKCGYDAGLY--SRSAK  
 HFZ5 ECPAGGPFV-----CKCREPFVPILKESHPLYNKVRTGQVPNCAPVPCYQPSFSADER  
 HFZ6 VQRDIG-----FWCPRHLKTSGGQGYKFLGIDQCAPP CP---NMYFK--SDEL  
 MFZ6 VPRDIG-----FWCPKHLRTSGDQGYRFLGIEQCAPP CP---NMYFK--SDEL  
 HFZ7 ASDGRGRPAF-----PFSCPRQLKVPYLYGRLGERDCGAPCEPGRANGLMYFKEER  
 MFZ7 -SDGRGRLSF-----PFSCPRQLKVPYLYGRLGERDCGAPCEPGRANGLMYFKEER  
 HFZ8 ARPPGGGAAP---CEPGCQCRAPMVSVSSERHPLYNRVKTGQIANCALPCHNPFSSQDER  
 MFZ8 ARPPGGGAAP---CEPGCQCRAPMVSVSSERHPLYNRVKTGQIANCALPCHNPFSSQDER  
 HFZ9 PRPARPPG-----DLGPAGGSGTCENPEKFQYVEKSRSCAPRCGPGVEVFWSSRDK  
 MFZ9 PRPARPPG-----DSAPGPGSGGTCDNPEKFQYVEKSRSCAPRCGPGVEVFWSSRDK  
 HFZ10 FRPQRPHSAQ---EHPLKDGGPGRGCDNPGKFHHVEKSASCAPLCTPGVDVYWSREDK

T.D. 103-050101

HFZ1 RFSRTWIGIWSVLCCASTLFTVLTYLVDMMRRFSYPERPIIFLSGCTAVAVAYIAGFLLE  
 MFZ1 RFSRTWIGIWSVLCCASTLFTVLTYLVDMPRFSYPERPIISLSGCTAVAVAYIAGFLLE  
 HFZ2 RFARLWILTWSVLCCASTFTFTVTLTYLVDMMRRFSYPERPIIFLSGCTMVSVAIYIAGFVLQ  
 HFZ3 SFARYFIGLISIIICLSATLFTFTLFLIDVTRFRYPERPIIFYAVCYMMVSLIFFIGFLLE  
 MFZ3 SFARYFIGLISIIICLSATLFTFTLFLIDVTRFRYPERPIIFYAVCYMMVSLIFFIGFLLE  
 HFZ4 EFTDIWMAVWASLFCFISTFTVTLTFLIDSSRFSYPERPIIFLSMCYNIYSIAYIVRLTVG  
 MFZ4 EFTDIWMAVWASLFCFISTFTVTLTFLIDSSRFSYPERPIIFLSMCYNIYSIAYIVRLTVG  
 HFZ5 TFATFWIGLWSVLCFISTFTVTLTFLIDMDTFRYPERPIIFLSACYLVCVSLGFLVRLVVG  
 HFZ6 EFAKSFIGTVSIFCLCATLFTFTLFLIDVRRFRYPERPIIYYSVCSIVSLMYFIGFLLG  
 MFZ6 DFAKSFIGTVSIFCLCATLFTFTLFLIDVRRFRYPERPIIYYSVCSIVSLMYFVGFLLG  
 HFZ7 RFARLVWGVWSVLCCASTLFTVLTYLVDMMRRFSYPERPIIFLSGCTFMVAHVAGFLLE  
 MFZ7 RFARLVWGVWSVLSCASTLFTVLTYLVDMMRRFSYPERPIIFLSGCTFMVAHVAGFLLE  
 HFZ8 AFTVFWIGLWSVLCFVSTFATVSTFLIDMERFKYPERPIIFLSACYLFVSVGYLVRLVAG  
 MFZ8 AFTVFWIGLWSVLCFVSTFATVSTFLIDMERFKYPERPIIFLSACYLFVSVGYLVRLVAG  
 HFZ9 DFALVWMAVWSALCFSTFTVTLTFLLEPHRFQYPERPIIFLSMCYNVYSLAFLIRAVAG  
 MFZ9 DFALVWMAVWSALCFSTFTVTLTFLLEPHRFQYPERPIIFLSMCYNVYSLAFLIRAVAG  
 HFZ10 RFAVVWLAIWAVLCCFSSAFTVTLTFLIDPARFRYPERPIIFLSMCYCVSVGYLIRLFAAG

\*: :: : : : \* \*: : : \* \* \* \* \* : \* \* : : ..

→ extracellular domain loop 1

HFZ1 DRVVCNDK-----FAEDGARTVAQGTCK  
 MFZ1 DRVVCNDK-----FAEDGARTVAQGTCK  
 HFZ2 ERVVCNER-----FSEDGYRTVVQGTCK  
 HFZ3 DRVACNAS-----I---PAQYKASTVTQGSKN  
 MFZ3 DRVACNAS-----S---PAQYKASTVTQGSKN  
 HFZ4 RERISCDF-----EEAAEPVLIQEGLEK  
 MFZ4 RERISCDF-----EEAAEPVLIQEGLEK  
 HFZ5 HASVACS-----RE-----HNHIHYETTGP  
 HFZ6 DSTACNKA-----D---EKLELGDVTVLGSKN  
 MFZ6 NSTACNKA-----D---EKLELGDVTVLGSKN  
 HFZ7 DRAVCVER-----FSDDGYRTVAQGTCK  
 MFZ7 DRAVCVER-----FSDDGYRTVAQGTCK  
 HFZ8 HEKVACSGGAPGAGGAGGAGGAAA-GAGAAGAGAGGPGGRGEYELGAVEQHVRVYETTGP  
 MFZ8 HEKVACSGGAPGAGGRGGAGGAAAAGAGAAGRGASSPGARGEYELGAVEQHVRVYETTGP  
 HFZ9 AQSVACD-----QEAGALYVIQEGLEN  
 MFZ9 AQSVACD-----QEAGALYVIQEGLEN  
 HFZ10 AESIACD-----RDSGQLYVIQEGLES

←

HFZ1 EGCTILFMMLYFFSMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAIKT  
 MFZ1 EGCTILFMMLYFFSMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAIKT  
 HFZ2 EGCTILFMMLYFFSMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAVKT  
 HFZ3 KACTMLFMILYFFTMAGSVWWVILTITWFLAAVPKWGSEAEIKKALLFHASAWGIPGTLT  
 MFZ3 KACTMLFMVLYFFTMAGSVWWVILTITWFLAAVPKWGSEAEIKKALLFHASAWGIPGTLT  
 HFZ4 TGCAIIFLLMYFFGMASSIWWVILTLTWFLAAGLKWGHEAIEMHSSYFHIAAWAIPAVKT  
 MFZ4 TGCAIIFLLMYFFGMASSIWWVILTLTWFLAAGLKWGHEAIEMHSSYFHIAAWAIPAVKT  
 HFZ5 ALCTIVFLLVYFFGMASSIWWVILSLTWFLAAGMKWGNEAIEAGYSQYFHLAAWLIPSVKS  
 HFZ6 KACTVLFMLLYFFTMAGTVWWVILTITWFLAAGRKWSCEAIEQKAVWFHAVAWGTPGFLT  
 MFZ6 KACSVMFLYFFTMAGTVWWVILTITWFLAAGRKWSCEAIEQKAVWFHAVAWGAPGFLT  
 HFZ7 EGCTILFMVLYFFGMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAVKT  
 MFZ7 EGCTILFMVLYFFGMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAVKT  
 HFZ8 ALCTVFLVLYFFGMASSIWWVILSLTWFLAAGMKWGNEAIEAGYSQYFHLAAWLIPSVKS  
 MFZ8 ALCTVFLVLYFFGMASSIWWVILSLTWFLAAGMKWGNEAIEAGYSQYFHLAAWLIPSVKS  
 HFZ9 TGCTLVFLLLYFFGMASSLWVVLTITWFLAAGKKWGHEAIEAHGSYFHLAAWGLPALKT  
 MFZ9 TGCTLVFLLLYFFGMASSLWVVLTITWFLAAGKKWGHEAIEAHGSYFHLAAWGLPALKT  
 HFZ10 TGCTLVFLVLYFFGMASSLWVVLTITWFLAAGKKWGHEAIEANSYFHLAAWIPAVKT

\*: : : : : \* \* : : : \* \* \* \* \* \* \* \* \* \* \* \* \* \* \* \* \* \* :

→ extracellular domain loop 2 ←

HFZ1 ITILALGQVDGDLVSGVCFVGLNNVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRITI  
 MFZ1 ITILALGQVDGDLVSGVCFVGLNNVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRITI  
 HFZ2 ITILAMGQIDGDLVSGVCFVGLNLDPLRGFVLAPLFVYLFIGTSFLLAGFVSLFRITI  
 HFZ3 IILLAMNKIEGDNISGVCVGLYDVALRYFVLAPLCYVVGVSLLLAGIISLNRVRIE  
 MFZ3 IILLAMNKIEGDNISGVCVGLYDVALRYFVLAPLCYVVGVSLLLAGIISLNRVRIE

Figure 8d

## |→ extracellular domain loop 2 ←|

HFZ4 IVILIMRLVDADELTLGLCYVGNQNLDAITGTFVVAFLFTYLVIGTLFIAAGLVALFKIRSN  
 MFZ4 IVILIMRLVDADELTLGLCYVGNQNLDAITGTFVVAFLFTYLVIGTLFIAAGLVALFKIRSN  
 HFZ5 ITALALSSVDGDPVAGICYVGNQNLNSLRRLVGLPLVLYLLVGTLLAGFVSLFRIRSV  
 HFZ6 VMLLAMNKVEGDNISGVCVGLYDLASRYFVLLPLCLCVFVGLSLLLAGIISLNHVRQV  
 MFZ6 VMLLAMNKVEGDNISGVCVGLYDLASRYFVLLPLCLCVFVGLSLLLAGIISLNHVRQV  
 HFZ7 ITILAMGQVDGDLISGVCVGLSSVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI  
 MFZ7 ITILAMGQVDGDLISGVCVGLSSVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI  
 HFZ8 IAVLALSSVDGDPVAGICYVGNQSLDNLRGFVLAPLVIYLFIGTMFLLAGFVSLFRIRSV  
 MFZ8 IAVLALSSVDGDPVAGICYVGNQSLDNLRGFVLAPLVIYLFIGTMFLLAGFVSLFRIRSV  
 HFZ9 IVILTLRKVAGDELTLGLCYVASTDAAALTGFVLVPLSGYLVGLSSFLLTGFVALFHIRKI  
 MFZ9 IVVLTLRKVAGDELTLGLCYVASTDAAALTGFVLVPLSGYLVGLSSFLLTGFVALFHIRKI  
 HFZ10 ILILVMRRVAGDELTLGVCYVGSMDVNALTGFVLIPLACYLVIGTSFILSGFVALFHIRRV  
 : \* : : . \* : : \* : : . \* : : \* : : \* : : \* : : \*

## |→ extracellular domain loop 3

HFZ1 MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVIACYFYEQAFRDQWERSWVAQSCKSY  
 MFZ1 MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVIACYFYEQAFRDQWERSWVAQSCKSY  
 HFZ2 MKH--DGTKTEKLERLMVRIGVFSVLYTVPATIVIACYFYEQAFREHWERSWVSQHCKSL  
 HFZ3 IPL--EKENQDKLVKFMIRIGVFSILYLVPLLVVIGCYFYEQAYRGIWETTWIQERCREY  
 MFZ3 IPL--EKENQDKLVKFMIRIGVFSILYLVPLLVVIGCYFYEQAYRGIWETTWIQERCREY  
 HFZ4 LQK--DGTKTDKLERLMVKIGVFSVLYTVPATCVIACYFYEISNWALFRYSADDSNMAV-  
 MFZ4 LQK--DGTKTDKLERLMVKIGVFSVLYTVPATCVIACYFYEISNWALFRYSADDSNMAV-  
 HFZ5 IKQ--GGTKTDKLEKLMIRIGIFTLLYTVPASIVVACYLYEQHYRESWEAALTCACPGHD  
 HFZ6 IQH--DGRNQEKLLKFMIRIGVFSGLYLVPLVTLGLCYVYELVNRITWETWVSDFHCRQY  
 MFZ6 IQH--DGRNQEKLLKFMIRIGVFSGLYLVPLVTLGLCYVYELVNRITWETWVSDFHCRQY  
 HFZ7 MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVLACYFYEQAFREHWERTWLLQTCKSY  
 MFZ7 MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVLACYFYEQAFREHWERTWLLQTCKSY  
 HFZ8 IKQDGPPTKTHKLEKLMIRLGLFTVLYTVPAAVVVACLFYEQHNRPRWEATHNCPCLRDL  
 MFZ8 IKQDGPPTKTHKLEKLMIRLGLFTVLYTVPAAVVVACLFYEQHNRPRWEATHNCPCLRDL  
 HFZ9 MKT--GGTNTKLEKLMVKIGVFSILYTVPATCVIVCYVYERLNMDFWRLRATEQPCTAA  
 MFZ9 MKT--GGTNTKLEKLMVKIGVFSILYTVPATCVIVCYVYERLNMDFWRLRATEQPCTAA  
 HFZ10 MKT--GGENTDKLEKLMVRIGLFSVLYTVPATCVIACYFXEHLNMDYWKILAAQHKCKM-  
 : : . \* : : \* : : \* : : \* : : \* : : \* : : \*

## ←|

HFZ1 AIPCPHLQAGGGAPPHPPMSPDFTVFMIKYLMTLIVGITSGFWIWSGKTLNSWRKFYTRL  
 MFZ1 AIPCPHLQAGGGVPPPHPPMSPDFTVFMIKYLMT-----LNSWRKFYTRL  
 HFZ2 AIPCP-----AHYTPR--MSPDFTVYMIKYLMTLIVGITSGFWIWSGKTLNSWRKFYTRL  
 HFZ3 HIPCP-----YQVTQMSRPDLILFLMKYLMALIVGIPSVFVWVGSKKTCFEWASFFHGR  
 MFZ3 HIPCP-----YQVTQMSRPDLILFLMKYLMALIVGIPSVFVWVGSKKTCFEWASFFHGR  
 HFZ4 -----EMLKIFMSLLVGITSGMWIWSAKTLHTWQ--KCSNR  
 MFZ4 -----EMLKIFMSLLVGITSGMWIWSAKTLHTWQ--KCSNR  
 HFZ5 TGQPR----AK-----PEYWVLMKYFMCLVVGITSGVWVWSGKTVESWRRFTSRC  
 HFZ6 HIPCP-----YQAKAKARPELALFMIKYLMTLIVGISAVFVWVGSKKTCFEWAGFFKRN  
 MFZ6 RIPCP-----YQANPKARPELALFMIKYLMTLIVGISAVFVWVGSKKTCFEWAGFFKRN  
 HFZ7 AVPCP----PGHFPPM---SPDFTVFMIKYLMTMIVGITTGFVWWSGKTLQSWRRFYHRL  
 MFZ7 AVPCP----PRHFSPM---SPDFTVFMIKYLMTMIVGITTGFVWWSGKTLQSWRRFYHRL  
 HFZ8 QPDQA----RR-----PDYAVFMLKYFMCLVVGITSGVWVWSGKTLESWRSLCTRC  
 MFZ8 QPDQA----RR-----PDYAVFMLKYFMCLVVGITSGVWVWSGKTLESWRSLCTRC  
 HFZ9 AGPGG----RRDCSLPGGSVPTVAVFMLKIFMSLVVGITSGVWVWSKTFQTWQSLCYRK  
 MFZ9 TVPGG----RRDCSLPGGSVPTVAVFMLKIFMSLVVGITSGVWVWSKTFQTWQSLCYRK  
 HFZ10 NNQTK----TLDC--LMAASIPAVEIFMVKIFMLLVVGITSGMWIWTSTLQSWQVCSRR  
 : : \* : : \*

HFZ1 TN--SKQGETTV-----  
 MFZ1 TN--SKQGETTV-----  
 HFZ2 TN--SRHGETTV-----  
 HFZ3 RKKEIVNESRQVLQEP-----DFAQSLLRDPNTPIIRKSRGTSTQGTSTHAS  
 MFZ3 RKKEIVNESRQVLQEP-----DFAQSLLRDPNTPIIRKSRGTSTQGTSTHAS  
 HFZ4 LVNSGKVKREKRGNGW-----VKPGKGSE-----  
 MFZ4 LVNSGKVKREKRGNGW-----VKPGKGNE-----  
 HFZ5 CC--RPRRGHKSGGA-----MA--AG-D-----  
 HFZ6 RKRDPISESRRVLQESCEFFLKHNKSVKHKKKHYKPSHKLKVISKSMGTSTGATANHGT  
 MFZ6 RKRDPISESRRVLQESCEFFLKHNKSVKHKKKHGAPGPHRLKVISKSMGTSTGATTNHGT

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Figure 8e

HFZ7	SH--SSKGETAV-----
MFZ7	SH--SSKGETAV-----
HFZ8	CW-ASKGAAVGGGAGA-----TAAGGGGGPGGGGGGGP
MFZ8	CW-ASKGAAVGGAGAGG-----SGPGGSGP-----GP
HFZ9	IA--AGRARAKACRAP-----GSYGRGTHC-----
MFZ9	MA--AGRARAKACRTP-----GGYGRGTHC-----
HFZ10	LKKKSRRKPASVITSG-----GIYKKAQH-----

HFZ1	-----
MFZ1	-----
HFZ2	-----
HFZ3	STQLAMVDDQRSKAGSIHISKVSSYHGSLHRSRDGRYTPCSYRG--MEERLPHGSMS-RLT
MFZ3	STQLAMVDDQRSKAGSVHISKVSSYHGSLHRSRDGRYTPCSYRG--MEERLPHGSMS-RLT
HFZ4	-----TVV-----
MFZ4	-----TVV-----
HFZ5	-----YPEASAALTGRTGPPGPAATYHKQVSLSHV-----
HFZ6	SAVAITSHDYLGOETLITEIQTSPETSMREVKADGASTPRLREQDCGEPASPAASIS-RLS
MFZ6	SAMAIADHDYLGQETSTEVHTSPEASVKEGRADRANTPSAKDRDCGESAGPSSKLSGNRN
HFZ7	-----
MFZ7	-----
HFZ8	GGGGGPGGGGSLYSDVSTGLTWRSGTAS-SVSYPKOMPLSQV-----
MFZ8	GGGGGHGGGGSLYSDVSTGLTWRSGTAS-SVSYPKOMPLSQV-----
HFZ9	-----H--YKAPTIVLHMTKTDPSLENPTHL-----
MFZ9	-----H--YKAPTIVLHMTKTDPSLENPTHL-----
HFZ10	-----PQKT-HHGKYEIPAQSPTCV-----

HFZ1	-----
MFZ1	-----
HFZ2	-----
HFZ3	DHSRHSSSHRLNEQSRHSSIRDLSNNPMTHITHGTSMNRVIEEDGTSA-----
MFZ3	DHSRHSSSHRLNEQSRHSSIRDLSNNPMTHITHGTSMNRVIEEDGTSA-----
HFZ4	-----
MFZ4	-----
HFZ5	-----
HFZ6	GEQVDGKG--QAGSVSESARSEGRISPKSDITDTGLAQSNLQVPSSEPSLKGSTSL
MFZ6	GRESRAGGLKERSNGSEGAPSEGRVSPKSSVPETGLIDCSTSQAASSPEPTSLKGSTSLP
HFZ7	-----
MFZ7	-----
HFZ8	-----
MFZ8	-----
HFZ9	-----
MFZ9	-----
HFZ10	-----

HFZ1	-----
MFZ1	-----
HFZ2	-----
HFZ3	-----
MFZ3	-----
HFZ4	-----
MFZ4	-----
HFZ5	-----
HFZ6	VHPVSGVRKEQGGGCHSDT
MFZ6	VHSASRARKEQGAGSHSDA
HFZ7	-----
MFZ7	-----
HFZ8	-----
MFZ8	-----
HFZ9	-----

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